

REMARKS

Claims 1-32 are pending and have been rejected. Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow. The specification has been amended to include a reference to applicant's prior application. Claims 1-32 remain in the case.

Claims 1-11, 17-26 and 30-32 are rejected under the first paragraph of Section 112. A very similarly-worded rejection was raised on April 24, 2003. Via a response filed on July 24, 2003, applicant introduced new claims 32 and 33, in addition to submitting extensive evidence countering the basis for rejection. In the next communication, the examiner added claim 32 to the non-enablement rejection, but indicated that claim 33 was objected to only for its dependency on a rejected base claim. In order to advance prosecution, applicant amended claim 1 to incorporate the recitation of claim 33, thereby placing it in *prima facie* condition for allowance.

Nevertheless, the examiner continues to reject claim 1 for lack of enablement. The rationale for rejection is narrowed, however, to whether polynucleotide vectors other than MnSOD, gamma-GTP, and metallothionein are enabled; hence, claims 12-16 are deemed allowable. Still, the examiner has ignored extensive evidence and commentary on point, provided with applicant's responses of January 9, 1997, January 23, 1997, and July 24, 2003. Furthermore, applicant forwards with this response a declaration of Dr. Chandra Belani, which was submitted in applicant's copending case, SN 09/075,532.

In the aforementioned responses filed in 1997, applicant submitted and discussed the declaration under Rule 132 of Dr. Michael Lotze. Dr. Lotze is an expert in the field of gene therapy, having over 18 years experience in cellular immunology and over 9 years experience in human gene therapy. He also has served on the editorial boards of 14 peer-reviewed scientific journals, including several that specifically concern gene therapy.

In his declaration Dr. Lotze attests that those skilled in the art of gene therapy could use Dr. Greenberger's data on polynucleotides encoding Cu/ZnSOD and MnSOD to assess polynucleotides other than the gamma glutamyl transpeptidase, manganese superoxide

dismutase, metallothionein or copper/zinc superoxide dismutase. More particularly, he notes that the data on Cu/ZnSOD or MnSOD could easily be applied to other radiation protection gene products that interact with toxic species, such as catalase, α 1-antitrypsin, bleomycin hydrolase, peroxidases such as glutathione peroxidase) and proteases.

At the time of submission of the Lotze declaration in 1997, the only "rebuttal" by the examiner of the statements made by Dr. Lotze with respect to the scope of the polynucleotide was not factual, but entailed only a citation to case law. Thus, the examiner urged that "the broad scope of agents has not been enabled insofar as therapeutic gene transfer is concerned. With respect to a prima facie case of nonenablement, while a single embodiment may provide broad enablement in cases involving predictable factors, such as physiological activity, *a further showing is required.* (*In re Fisher*, 166 USPQ 18 (CCPA 1970)).

Applicant's submission of a declaration by Dr. Lotze, who clearly is in an expert in this field, constitutes a "further showing" within the context of *In re Fisher*. (No factual basis is preferred to substantiate the examiner's opinion that the claims are not enabled with respect to polynucleotides. Accordingly, Dr. Lotze's expert opinion is unrebutted in the record.

Dr. Chandra Belani echoes Dr. Lotze's comments. He attests that a variety of proteins that eliminate toxic species, selected from the group consisting of free radicals, superoxide anions and heavy metal cations, are known to the skilled artisan and also would be expected to work in the context of the present method. Suitable proteins include not only MnSOD, gamma-glutamyl transpeptidase, and metallothionein, but also glutathione peroxidase, catalase, and other agents which might block radiation-induced apoptosis, including BCL-XL, antisense BCL-2, antisense BAX. Furthermore, he notes that the selection of suitable promoters for these proteins would be within the level of skill in the art and would not require undue experimentation.

In addition to Dr. Belani's declaration, appended are abstracts from articles located on Pub Med, each of which reports successful transfection of cells with other of the genes mentioned in Dr. Belani's declaration, such as bcl-2, bax, glutathione peroxidase, and

catalase. These articles show successful transfection according to the invention with other genes within the scope of "a polynucleotide that encodes a protein capable of neutralizing or eliminating toxic species selected from the group consisting of a free radical, a superoxide anion, and a heavy metal cation." They likewise show that these genes are associated with free radicals, particularly reactive oxygen species such as hydrogen peroxide. Accordingly, the scope of applicant's claims with respect to the transgene is fully enabled.

It is noted that, following submission of the Belani declaration and appended articles, that Examiner Chen allowed method claims with a scope that recited "a polynucleotide that encodes a protein that is transiently expressed in said subject, wherein said protein is capable of neutralizing or eliminating said toxic species." The toxic species is "selected from the group consisting of a free radical, a superoxide anion and a heavy metal cation." The presently submitted evidence, along with the evidence previously submitted, clearly supports applicant's presumptively accurate disclosure that the present invention is supported across the full scope of that which is claimed. Accordingly, reconsideration and withdrawal of this ground of rejection is respectfully requested.

Claim 27 is rejected under Section 102(b) based on Cousens *et al.* (US 4,751,180). Claim 27 recites a pharmaceutical composition comprising a polynucleotide that encodes a protein such that the protein is transiently expressed in a subject exposed to an agent that elicits production of a toxic species that is a free radical, a superoxide anion, or a heavy metal cation, wherein the protein is capable of neutralizing or eliminating the toxic species; and a pharmaceutically acceptable vehicle for the polynucleotide. The examiner urges that Cousens *et al.* teaches construction of a yeast expression plasmid pYSII containing the human SOD gene fused to the N-terminal of human proinsulin gene under control of GAP promoter, and that "the TE buffer is considered a pharmaceutically acceptable vehicle."

The TE buffer of Cousens *et al.* comprises 10 mM Tris, 1 mM EDTA, pH 8.0. Tris buffer is widely used in laboratory applications such as *in situ* hybridization, *in vitro* diagnostic assays, and as an electrophoresis buffer, as shown in the appended items located during an online search. Contrary to the examiner's allegation, however, a skilled artisan would not consider Tris buffer to be a pharmaceutically acceptable vehicle.

Moreover, the skilled artisan would not construe a yeast expression plasmid in Tris buffer to be "a pharmaceutical composition." A yeast expression plasmid would not be used in a pharmaceutical composition, since the term means that the composition is suitable for use *in vivo*. A yeast expression plasmid is used to transfect yeast cells so that the product encoded by the plasmid can be expressed and collected. This is indeed the purpose of the yeast expression plasmid in Cousens *et al.*, which use the plasmids to for preparing a polypeptide in a cellular host and then isolating the fusion polypeptide in high yield. See abstract and claim 1. Use as the active ingredient in a pharmaceutical composition is not disclosed, nor would it be contemplated by a person reading Cousens *et al.*

Claims 27 and 28 are rejected under Section 102(b) based on Hartman *et al.* N/L (EP 0284105) or Ishiye *et al.* (*FEMS Microbiology Letters*, 1992). The examiner states that Hartman teaches construction of a plasmid pMSE-4 containing a human manganese superoxide dismutase (hMnSOD) coding region under the control of lambda P_L promoter, and use of said plasmid to transfect *E. coli* cells for producing recombinant hMnSOD.

Once again, the examiner argues that "***the*** buffer solution for the plasmid is considered a pharmaceutically acceptable vehicle." A careful reading of Hartman shows no composition of polynucleotide in a buffer. The only buffer mentioned is in Example 1, and is used to wash filters that contain immobilized phage plaques. It is Example 2 that relates to the expression plasmid, and no buffer is mentioned. In a similar rejection, the examiner argues that "Ishiye *et al.* teaches construction of an expression vector containing coding sequences of *E. coli* HB101 gamma-glutamyltranspeptidase (GGT) and use of said plasmid to produce recombinant GGT protein. ***The*** buffer solution containing the expression vector expressing GGT is considered a pharmaceutically acceptable vehicle." As in Hartman *et al.*, there is no disclosure of the plasmid in a buffer. Characterization of undisclosed buffers in Hartman and Ishiye as pharmaceutically acceptable vehicles indicates the extent of the examiner's hindsight reconstruction of applicant's invention.

Moreover, even were Hartman or Ishiye to disclose their expression plasmids in a buffer, a skilled artisan would not interpret this as "a pharmaceutical composition." The expression plasmids of Hartman and Ishiye would not be used in a "pharmaceutical

composition," a term which means that the composition is suitable for use *in vivo*. The expression plasmids of Ishiye are used to transfect *E. coli* cells so that the product encoded by the plasmid can be expressed and collected. Hartman *et al.*, disclose expression plasmids for expression in either prokaryotic (*E. coli* cells) or eukaryotic (human cell lines). The disclosure in either of these references of plasmids for manufacturing the encoded protein does not anticipate a claim directed to a pharmaceutical composition that contains the polynucleotide as the active ingredient, in combination with a pharmaceutically acceptable vehicle. In other words, a knowledgeable person would not understand Hartman *et al.* or Ishiye *et al.* to disclose a pharmaceutical composition as presently claimed.

Claims 27 and 29 are rejected under Section 102(b) based on Hartman *et al.* (EP 0284105) in view of Nabel *et al.* (*Annals New York Academy of Sciences*, 1994). The examiner's interpretation of Hartman, and applicant's rebuttal of that characterization are provided above. The examiner relies on Nabel *et al.* as teaching the use of retrovirus, adenovirus, adenoviral conjugates, and cationic liposomes for delivery of foreign DNA into vascular cells *in vivo*. A skilled artisan would not have been motivated to formulate the expression vector of Hartman for delivery *in vivo*, however, because Hartman only teaches use of the recombinant **protein product** of this expression vector *in vivo*. The expression vector is only used to produce recombinant MnSOD, which is then recovered and formulated for therapeutic use (page 21, lines 7-9). Formulation of the **polynucleotide** itself as a pharmaceutical composition is not suggested.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to

Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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